

CLAIMS

What is claimed is:

1. An agent which inhibits nitric oxide synthase by blocking calmodulin activation of the nitric oxide synthase.
- 5 2. The agent of Claim 1, which specifically inhibits a constitutive nitric oxide synthase.
3. The agent of Claim 2, which specifically inhibits endothelial nitric oxide synthase.
4. The agent of Claim 2, which specifically inhibits neuronal nitric oxide synthase.
- 10 5. The agent of Claim 1, which specifically inhibits inducible nitric oxide synthase.
6. A nitric oxide synthase inhibitor peptide, comprising at least two positively charged amino acids selected from the group consisting of: arginine, histidine, lysine, and ornithine.
- 15 7. The peptide of Claim 6, comprising the amino acid sequence RRKRK (SEQ ID NO. 8). *not correct SEQ ID NO.*
8. The peptide of Claim 7, comprising the amino acid sequence of SEQ ID NO. 1 or an inhibitory fragment thereof.
9. The peptide of Claim 7, wherein the peptide binds to a site spatially adjacent to the calmodulin binding site of endothelial nitric oxide synthase.

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10. The peptide of Claim 7, comprising the amino acid sequence of SEQ ID NO. 1 or a fragment or derivative thereof, wherein the derivative has one or more amino acids deleted or inserted, or has one or more conservative substitutions.
11. The peptide of Claim 7, wherein the peptide has an amino acid sequence
5 selected from the group consisting of: WRRKRK (SEQ ID NO. 12);
SSWRRKRKES (SEQ ID NO. 13);
SSPRPEQHKSYKIRFNSVSCSDPLVSSWRRKRKES (SEQ ID NO. 14); and
QHKSYPKIRFNSVSCSDPLVSSWRRKRKE (SEQ ID NO. 15).
12. A nitric oxide synthase inhibitor peptide comprising the amino acid sequence of
10 SEQ ID NO. 2 or a fragment or derivative thereof, wherein the derivative has one or more amino acids deleted or inserted, or has one or more conservative substitutions.
13. The peptide of Claim 12, wherein the peptide binds to a site spatially adjacent to the calmodulin binding site of neuronal nitric oxide synthase.
14. The peptide of Claim 12, wherein the peptide has an amino acid sequence
15 selected from the group consisting of: QEERKSYKVRF (SEQ ID NO. 16),
RPEQHKSYKIRF (SEQ ID NO. 17), SDSRKSSGDGPDLR (SEQ ID NO. 18),
and QEERKSYKVRFNSVSSYSDSQKSSGDGPD (SEQ ID NO. 19).
15. A nitric oxide synthase inhibitor peptide comprising the amino acid sequence of
20 SEQ ID NO. 2, or a fragment thereof.
16. An activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein

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17. An antibody which binds to one or more amino acids between about amino acids 590-650 of endothelial nitric oxide synthase.
18. The antibody of Claim 17, wherein the antibody activates endothelial nitric oxide synthase.
19. A constitutive nitric oxide synthase activator peptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, and activating fragments and derivatives of SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9.
20. An activator of neuronal nitric oxide synthase which antagonizes autoinhibition by a peptide region of neuronal nitric oxide synthase, wherein the region is between about amino acids 820-880 of neuronal nitric oxide synthase.
21. An antibody which binds to one or more amino acids between about amino acids 820-880 of neuronal nitric oxide synthase.
22. The antibody of Claim 21 wherein the antibody activates neuronal nitric oxide synthase.
23. An antibody which binds to one or more amino acids in a peptide having an amino acid sequence selected from the group consisting of: SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, and SEQ ID NO. 9.

24. The antibody of Claim 23, wherein the antibody is a monoclonal antibody or a fragment thereof.
25. An isolated nucleic acid encoding the antibody of Claim 24.
26. A method of inhibiting a nitric oxide synthase, comprising contacting the nitric oxide synthase with an effective amount of an agent of Claim 1.
27. A method of inhibiting endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 3.
28. A method of inhibiting neuronal nitric oxide synthase, comprising contacting the neuronal nitric oxide synthase with an effective amount of an agent of Claim 4.
29. A method of inhibiting a constitutive nitric oxide synthase, comprising contacting the nitric oxide synthase with an effective amount of an agent of Claim 7.
30. A method of inhibiting a constitutive nitric oxide synthase, comprising contacting the nitric oxide synthase with an effective amount of an agent of Claim 8.
31. A method of activating endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 16.

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32. A method of activating endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 19. *SEQ ID NO. 4-9 and 17-20*

33. A method of activating neuronal nitric oxide synthase, comprising contacting the neuronal nitric oxide synthase with an effective amount of an agent of Claim 20. *826-827, 829-830, 832-833*

34. An agent which inhibits inducible nitric oxide synthase by blocking electron transfer from NADPH to an active site of nitric oxide synthase.

35. The agent of Claim 34, wherein the nitric oxide synthase is inducible nitric oxide synthase.

36. The agent of Claim 34, which binds to a site spatially adjacent to the calmodulin binding site of inducible nitric oxide synthase.

37. The agent of Claim 36, wherein the agent binds to one or more amino acids between about amino acids 600-615 of inducible nitric oxide synthase.

38. An activator of endothelial nitric oxide synthase which binds to one or more amino acids in a sequence selected from the group consisting of: SEQ ID NO. 21 and SEQ ID NO. 24.

39. An activator of inducible nitric oxide synthase which binds to one or more amino acids in a sequence selected from the group consisting of: SEQ ID NO. 3, SEQ ID NO. 22 and SEQ ID NO. 25.

40. An antibody which binds to one or more amino acids between about amino acids 600-615 of inducible nitric oxide synthase.

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41. The antibody of Claim 40, wherein the antibody inhibits inducible nitric oxide synthase.
42. The antibody of Claim 40, wherein the antibody activates inducible nitric oxide synthase.
- 5 43. A method of treating a disease modulated by the production of nitric oxide by endothelial nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 3.
44. A method of treating a disease modulated by the production of nitric oxide by neuronal nitric oxide synthase in a mammal, comprising administering to the
10 mammal an effective amount of an agent of Claim 4.
45. A method of treating a disease modulated by the production of nitric oxide by a constitutive nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 2.
46. A method of treating a disease modulated by the production of nitric oxide by a
15 constitutive nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 6.
47. A method of treating a disease modulated by the production of nitric oxide by a constitutive nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 8.
- 20 48. A method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 16.

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49. A method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 19. *See ID 4-6*

50. A method of treating a disease modulated by production of nitric oxide by neuronal nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 20. *8-20-2000*

51. A method for identifying an agent that modulates activity of a nitric oxide synthase, comprising assaying the ability of the agent to modulate calmodulin activation of the nitric oxide synthase.

52. The method of Claim 51, wherein the nitric oxide synthase is selected from the group consisting of: endothelial nitric oxide synthase, neuronal nitric oxide synthase, and inducible nitric oxide synthase.

53. The method of Claim 51, wherein the agent inhibits the activity of the nitric oxide synthase.

54. A method for identifying agents which modulate activity of a constitutive nitric oxide synthase, comprising assaying the ability of the agent to modulate autoinhibition of the nitric oxide synthase.

55. The method of Claim 54, wherein the constitutive nitric oxide synthase is selected from the group consisting of: endothelial nitric oxide synthase and neuronal nitric oxide synthase.

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56. A method for identifying an agent that modulates activity of a nitric oxide synthase, comprising assaying the ability of the agent to block electron transfer from NADPH to an active site of the nitric oxide synthase.
57. An isolated nucleic acid encoding the peptide of Claim 6 or a complement thereof.
58. An isolated nucleic acid encoding the peptide of Claim 12 or a complement thereof.
59. An isolated nucleic acid encoding the peptide of Claim 19 or a complement thereof.